

1 AP3 Rec'd PCT/PTO 16 JUN 2008

**THE USE OF CYSTINE OR CYSTEINE FOR THE PREVENTION AND
TREATMENT OF OXIDATIVE STRESS CAUSED BY
HAEMODIALYSIS AND OF ACUTE OR CHRONIC KIDNEY
DISEASES**

This invention relates to the use of cysteine and its disulphide oxidised form (cystine) to prepare oral medicinal products for the prevention and treatment of oxidative stress resulting from haemodialysis treatment in patients suffering from chronic kidney failure.

5 The invention also relates to the use of cysteine or cystine for the preparation of a medicament for the treatment and prevention of acute or chronic kidney diseases.

BACKGROUND OF THE INVENTION

Oxidative stress is defined as an imbalance between the physiological
10 systems of antioxidant protection and increased production of oxygen or nitrogen radicals by the cells of the immune system. The result can be damage to the molecular structure of proteins, sugars and lipids together with damage to the cell functions, which also prejudices the functions of the body's vital organs. Oxidative stress has been observed to be particularly evident in
15 patients suffering from kidney failure and undergoing haemodialysis. This phenomenon is attributed to bioincompatibility between the patient's circulating blood cells and the dialysis membranes, together with other factors such as a chronic uraemic state. This bioincompatibility leads to excessive production of Reactive Oxygen Species (ROS) by the immune system, and at
20 the same time a reduction in the antioxidant capacity of the body due to losses of antioxidant molecules such as glutathione (GSH), vitamin A, vitamin C and vitamin E through the filters of the dialysis membranes.

One of the consequences of this abnormal immune response is a

BESTÄTIGUNGSKOPIE

condition of oxidative stress, which leads to greater susceptibility to infection due to the defective immune response, amyloidosis and accelerated atherosclerosis due to continual activation of the immunocompetent cells. This triggers an inflammatory response, with consequent continual release of
5 cytokines and lysosomal proteolytic enzymes, and stimulation of free radical production; in practice the oxidative stress becomes a self-replicating process, and generates a condition of chronic inflammation.

The main consequence of oxidative stress is cardiovascular complications, which are the main cause of death in patients suffering from
10 chronic kidney failure. At local level these complications are manifested by alterations of the endothelium, accumulation of lipids, formation of clots and occlusion of the lumen.

At systemic level, chronic oxidative stress stimulates acute-phase protein synthesis by the liver at the expense of synthesis of other proteins,
15 such as albumin and transferrin: the result is malnutrition, which is exacerbated by catabolic breakdown of muscle proteins and reduced appetite.

The chronic renal failure (CRF) is a progressive disease of kidney; when the kidney has lost all its ability of clear the blood, the patients cannot survive and have to be submitted to the dialysis procedure. Such a last
20 condition is defined End-Stage Renal-Disease (ESRD).

Examples of the treatment of oxidative stress by administering products with antioxidant activity are reported below. The product most often used for the prevention and treatment of oxidative stress at present is N-acetylcysteine (see, for example, *Kidney Int.*, Vol 64 (2003), pp. 82-91; *Current Med. Chem.*,
25 2003, 10, pp. 1241-53). In particular, WO 01/02004 describes the use of N-acetylcysteine by intravenous injection before and/or during haemodialysis treatment.

According to Nakanishi et al., *Kidney Int.* 2003 Mar; 63(3): 1137-40,

the plasma concentration of cysteine and homocysteine increases in patients with chronic kidney failure who undergo dialysis. It consequently does not seem logical to further increase the cysteine concentration in these patients.

Santangelo F., *Current Med. Chem.*, 2003, 10, 2599-2610, has recently reviewed the therapeutic uses of cysteine pro-drugs such as N-acetylcysteine and its esters, thiazolidines, γ -glutamylcysteine and glutathione esters, particularly discussing the importance of intracellular GSH concentration. The oral administration of cysteine or cystine rather than derivatives thereof has been however neither disclosed nor suggested by this review.

10 DESCRIPTION OF THE INVENTION

The present invention involves the administration of cystine and/or cysteine for the prevention and treatment of oxidative stress resulting from haemodialysis treatment in patients suffering from chronic kidney failure.

According to a further embodiment, the invention also concerns the use of cystine and/or cysteine for the preparation of a medicament to be administered by the oral route for the treatment and prevention of chronic or acute kidney diseases as well as for the treatment and prevention of End-Stage renal Disease (ESRD).

The use of cysteine is preferred, but other substances known to have antioxidant properties, such as taurine, lipoic acid, and vitamins A, C and E, could also be added.

This invention therefore relates to oral compositions containing cystine and/or cysteine for the prevention and treatment of oxidative stress resulting from haemodialysis treatment in patients suffering from chronic kidney failure or for the treatment and prevention of acute or chronic kidney diseases or for the treatment and prevention of End-Stage renal Disease (ESRD).

These compositions will be prepared according to conventional methods well known in pharmaceutical technology, such as those described in

“Remington’s Pharmaceutical Handbook”, Mack Publishing Co., N.Y., USA.

This invention involves the oral administration of an effective quantity of cystine and/or cysteine before and/or after haemodialysis treatment in patients suffering from kidney failure. This quantity will depend on various factors, such as the severity of the condition and the patient’s weight. However, a unit dose will generally contain 200 to 1000 mg of cystine and/or cysteine. The compositions according to the invention will normally be administered before and/or after the haemodialysis treatment. These compositions are preferably administered in the form of compositions with an oral unit dose.

For the treatment and prevention of acute or chronic kidney diseases or for the treatment and prevention of End-Stage renal Disease (ESRD), the effective dose of cysteine or cystine ranges from 100 to 1000 mg, from 1 to 4 times a day.

According to a further aspect of the invention, the cystine or cysteine can be associated with non-toxic oral antioxidants, in particular vitamins A, C and E, lycopene, lipoic acid, ascorbic acid and taurine. Vitamin E and taurine are preferred.

According to the invention, the compositions may be in the form of tablets, capsules, oral preparations, powders, granules, lozenges, reconstitutable powders, syrups, solutions or suspensions. The solid compositions may contain conventional excipients, for example binders such as cellulose, mannitol and lactose; diluents, such as calcium carbonate, calcium phosphate and lactose; compression agents; lubricants such as magnesium stearate; disintegrants such as starch, polyvinylpyrrolidone and starch derivatives; colorants; flavouring agents and the like.

The liquid compositions may contain conventional excipients, for example suspending agents such as sorbitol, methylcellulose,

hydroxyethylcellulose and carboxymethylcellulose; preservatives, for example methyl or propyl p-hydroxybenzoate or sorbic acid, and conventional flavouring agents or colorants if desired.

The oral administration of cystine and/or cysteine offers considerable
5 advantages in terms of cost, ease and safety of administration compared with the use of intravenous and/or infusion formulations of N-acetylcysteine, which require skilled personnel for administration before dialysis treatment, and also involve the risk of contamination during dialysis.